Remarks

Reconsideration of this Application is respectfully requested.

Claims 1-5, 7-13 and 15-20 are pending in the application, with claim 1 being the independent claim. Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

I. Rejections under 35 U.S.C. § 103

A. Claims 1-5, 13 and 15-20

The Examiner rejected claims 1-5, 13 and 15-20 under 35 U.S.C. § 103(a) as allegedly being obvious over Jixian *et al.*, *Bull. Acad. Mil. Med. Sci. 21*:244-246 (1997) (hereinafter "Jixian") in view of Koch *et al.*, EP Application No. 0 513 738 A2 (hereinafter "Koch"). (*See* Office Action, page 2.) Applicants respectfully traverse this rejection, as the cited references clearly fail to teach or suggest the claimed invention.

1. The Claimed Invention

The present invention is directed to method for obtaining human erythropoietin comprising culturing mammalian cells which express recombinant human erythropoietin in culture medium consisting of DMEM (Dulbecco's modified Eagle's medium), F12 medium, insulin and one or more additives selected from the group consisting of $NaHCO_3$, sugars, ethanolamine, pyruvate, amino acids and mixtures thereof. Although the claimed method can include additional steps, by virtue of the phrase "consisting of," the claimed culture medium only includes the recited elements.

The claimed method provides for the massive culture of recombinant cells adequate for the industrial production of EPO. (*See* Specification, page 3, lines 25-26.) Importantly, the fact that the claimed invention does not employ any additional substances in the culture medium represents significant advantages. The use of fewer additives makes the method more economical and easier to perform, as there is a low concentration of contaminant proteins in the culture medium. This condition results in a high protein recovery ratio. (*See* Specification, page 3, line 27 to page 4, line 1.) The absence of further additives allows for an easier purification procedure and analysis of the obtained product, since additional substances can leave contaminants with the erythropoietin, which would require much more sophisticated purification systems to remove. The corresponding loss of efficiency of the process would likely result in the recovery of much less mass of erythropoietin. Moreover, the claimed method is advantageously reproducible and achieves high quality EPO regardless of the protein production scale. (*See* Specification, page 4, lines 3-4.)

2. Jixian

Jixian discloses the production of recombinant human erythropoietin using CHO cells in a serum-free medium containing insulin (SFM-p). *See* Abstract. Jixian further discloses that SFM-p comprises DMEM:F12 (1:1) medium and various additives including Se, lipid, vitamins, peptone, transferrin and cytokines. *See* Abstract. In particular, Jixian teaches that SFM-p contains, in addition to basal medium DMEM:F12, additive A (casein hydrolysate and yeast extract), additive B (Se, ethanolamine and fatty acids) and additive C (insulin, transferrin and growth factors). *See* Jixian translation,

page 4. Jixian teaches that additives A, B and C are required for the production of EPO at the level of 1% FBS:

> If type A, type B and type C additives were used in combination, the cell growth was significantly increased, showing increased cell count. (Table 2). The cell growth with the 3 additives was about the same compared with the case of 1% FBS.

Jixian translation, pages 4-5. As such, the experimental evidence of Jixian clearly teaches that the only way to obtain EPO production at the levels of 1% FBS is to include all components of medias A, B and C.

3. Koch

Koch discloses the production of erythropoietin in a serum-free culture medium containing insulin by cultivating genetically engineered CHO cells. In addition, Koch discloses that, besides insulin, there are other substances that can affect the growth of mammalian cells, such as transferrin. *See* Koch translation at page 2, paragraphs 1 and 2. According to Koch,

> The task of the invention . . . was to create a serum-free culture media for mammalian cells of a really quite general type that comes very close to the cultivation conditions when using a medium containing serum, but that does not contain any protein material of animal origin, which could present a danger of viral contamination. This task is solved by a serum-free medium for cultivation of mammalian cells without protein material of animal origin that contains, besides the usual ingredients, recombinant insulin from prokaryotes and a water-soluble iron compound, instead of animal insulin and transferrin.

Koch translation, page 2.

Therefore, in order to avoid the use of animal proteins which can be contaminated with pathogenic viruses, Koch employs a water soluble iron compound, such as iron citrate, iron sulfate, iron chloride or potassium hexacyanoferrate, instead of transferrin in the culture medium. Clearly, a critical aspect of the Koch disclosure, aside from the addition of recombinant insulin from prokaryotes, is the addition of a water-soluble iron compound as a transferrin substitute. *See* Koch translation at page 2 and claim 1.

4. Jixian and Koch Fail to Render the Claimed Invention Obvious

In order to establish a *prima facie* case of obviousness, all of the claim limitations must be taught or suggested by the prior art references. *See In re Royka*, 490 F.2d 981 (CCPA 1974). As demonstrated herein, Jixian and Koch clearly fail to teach or even suggest the claimed invention.

Applicants acknowledge that Jixian discloses "a culture media comprising DMEM and F12 (1:1) obtained from GIBCO-BRL containing the claimed media components $NaHCO_3$, sugars, ethanolamine sodium pyruvate and various amino acids." (Office Action, page 4.) However, in contrast to the disclosure of Jixian, the claimed culture medium does *not* include, for example, transferrin, yeast extract, fatty acids or casein hydrolysate as additives in addition to DMEM and F12 medium. Since the elements of the claimed culture medium are closed by virtue of the phrase "consisting of," and since Jixian discloses additional elements not recited in the claimed culture medium, the reference therefore fails to teach the claimed invention.

Koch clearly fails to remedy the deficiencies of Jixian. In contrast to the Koch disclosure, the present invention does not claim, among other things, a water-soluble iron compound as a substitute for transferrin in the culture medium (or even transferrin itself). At the very least, both Jixian and Koch teach that either transferrin (Jixian) or a substitute for transferrin (Koch) are required elements in the culture media. By virtue of the "consisting of" language employed in claim 1, the absence, for example, of transferrin or a water-soluble compound to substitute for transferrin, is in fact required in the rejected claims. As such, all of the claim limitations are not taught or suggested by the cited references.

Further, the present invention clearly requires fewer additives to obtain a high EPO recovery ratio than either Jixian or Koch. "[T]he omission of an element and retention of its function is an indicia of unobviousness." *In re Edge*, 359 F.2d 896, 149 USPQ 556 (CCPA 1966).

Not only do Jixian and Koch fail to teach or suggest all of the claim limitations, there is no suggestion or motivation, either in the cited references or in the knowledge generally available to one of ordinary skill in the art, to modify the references or combine reference teachings to obtain Applicants' invention. *See In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). The Examiner asserts that the rationale to modify the prior art is based upon mere routine optimization of the serum free culture media. (*See* Office Action, page 5.)

The claimed invention fills an unfulfilled need in the art. Specifically, "no method has yet been devised to produce efficiently EPO in industrial scale. The existent EPO culture systems are further characterized by their low reproducibility and output

quality." (Specification, page 2.) Thus, the claimed invention is not the result of routine optimization but rather is a substantial departure from the prior art and is not taught or suggested by the prior art.

The cited references disclose, at best, that one skilled in the art might find it "obvious to try" to produce the claimed invention. However, whether a particular combination might be "obvious to try" is not a legitimate test of patentability. *See In re Geiger*, 815 F.2d 686, 688 (Fed. Cir. 1987). When "what would have been 'obvious to try' would have been to . . . try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave . . . no direction as to which of many possible choices is likely to be successful," it would not have been obvious to produce the claimed invention. *See In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Accordingly, in view of the numerous possible culture medium ingredients and additives, as well as the limitless concentration possibilities, it is clear that it would *not* have been obvious to the skilled artisan to produce the claimed invention without the benefit of hindsight.

Moreover, a prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Not only do Jixian and Koch both fail to disclose all of the limitations of the claimed invention, but they in fact teach a person of ordinary skill in the art that there is *not* a reasonable expectation of success in producing recombinant EPO without transferrin or a substitute of transferrin as an extra source of iron in the cell

culture medium. "A prior art reference that 'teaches away' from the claimed invention is a significant factor to be considered in determining obviousness." MPEP § 2145.

Clearly, the claimed invention is not taught or suggested by the prior art references. Further, Applicants assert that there is neither a suggestion nor a motivation to modify the teachings to obtain Applicants' invention. Moreover, even assuming, *arguendo*, that such a suggestion or motivation to combine the references is present, there is no expectation of success in generating the claimed invention. Accordingly, it is respectfully requested that the rejection of claims 1-5, 7-13 and 15-20 under 35 U.S.C. § 103(a) be withdrawn.

B. Claims 7-10

The Examiner further rejected claims 7-10 under 35 U.S.C. § 103(a) as allegedly being obvious over Jixian and Koch in view of Yanagi *et al.*, *DNA 8*:419-427 (1989) (hereinafter "Yanagi") and Chiba *et al.*, U.S. Patent No. 3,865,801 (hereinafter "Chiba"). (*See* Office Action, page 5.) Applicants respectfully traverse this rejection.

The Examiner must demonstrate, *inter alia*, that all the claim limitations are taught or suggested by the prior art references in order to establish a *prima facie* case of obviousness. Claims 7-10 depend, either directly or indirectly, on claim 1, and therefore include all of the claim limitations of claim 1. *See* 35 U.S.C. § 112, paragraph 4. Applicants reassert that neither Yanagi nor Chiba remedy the deficiencies of Jixian and Koch, in that they, alone or in combination, fail to teach the claimed method.

Nevertheless, it is the Examiner's position that "applicant's arguments are found not prsuasive [sic] because as stated above the combined teaching Jixian and Koch

clearly suggest that [the claimed invention] is obvious to one of ordinary skill in the art with a reasonable expectation of success." (Office Action, page 7.) As demonstrated above, however, this argument is flawed as Jixian and Koch clearly do not teach or suggest the claimed invention. Therefore, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to claims 7-10 and respectfully request that this rejection be withdrawn.

C. Claims 7, 11 and 12

In addition, the Examiner rejected claims 7, 11 and 12 under 35 U.S.C. § 103(a) as allegedly being obvious over Jixian, Koch, Yanagi and Chiba and further in view of van Reis, U.S. Patent No. 5,490,937 (hereinafter "van Reis"). (*See* Office Action, page 7.) Applicants traverse this rejection as well.

As discussed above, the cited art references must teach or suggest all of the claim limitations in order to establish a *prima facie* case of obviousness. Claims 7, 11 and 12 depend, either directly or indirectly, on claim 1, and therefore include all of the claim limitations of claim 1. *See* 35 U.S.C. § 112, paragraph 4.

van Reis is directed to processes for separating compounds of interest from mixtures which comprise subjecting the mixture to tangential flow filtration where the filtration membrane has a specific pore size. As such, it is clear that van Reis fails to remedy the deficiencies of Jixian and Koch, in that it does not, alone or in combination with Yanagi or Chiba, teach the claimed method. Accordingly, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness of claims 7, 11 and 12 and respectfully request that this rejection be withdrawn.

II. Double Patenting

The Examiner rejected claims 1-13 and 15-20 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 7-13 of U.S. Patent No. 6,777,205. (*See* Office Action, page 9.)

Specifically, the Examiner asserted that

> [a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because the invention of US '205 is drawn to a method of producing EPO polypeptide, comprising culturing host cell (CHO, COS, BHK, Namalwa and HeLa) under conditions such that said polypeptide is expressed and recovered. Given the broadest reasonable interpretation to the culture conditions and recovery the method as claim[ed] in the US '205 [patent] encompasses the subject matter of claims 1-13, and 15-20 of [the] instant application.

(Office Action, page 9.)

Applicants respectfully disagree with the Examiner's assertion and note that claim 6 has been canceled and is therefore no longer pending in the present application. However, solely to advance prosecution, Applicants will submit a terminal disclaimer in accordance with 37 C.F.R. § 1.321(c) upon the notification by the Examiner of allowable subject matter.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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